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APPELLANTS' BRIEF Address to: Mail Stop Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Application Number	09/060,188
	Confirmation Number	9333
	Attorney Docket No.	AREN-001CIP
	Filing Date	April 14, 1998
	First Named Inventor	BEHAN, DOMINIC P.
	Examiner	HOWARD, ZACHARY C
	Group Art	1646
	Title: METHOD OF IDENTIFYING MODULATORS OF G-PROTEIN COUPLED RECEPTORS USEFUL IN THE TREATMENT OF DISEASE"OF DISEASE"	

Sir:

This Brief is filed in support of Appellants' appeal from the Examiner's Rejection dated September 11, 2009. No claims have been allowed, and Claims 34, 45-52, 61, 62, 69, 77, 79 and 81 are pending. Claims 34, 45-52, 61, 62, 69, 77, 79 and 81 are appealed. A Notice of Appeal was filed on March 8, 2010. In light of the enclosed petition for a 5 month extension of time, this Appeal Brief is timely filed.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

Provided herewith is an authorization to charge the amount of $540.00 to cover the fee required under 37 C.F.R. §41.20(b)(2) for filing Appellants' Brief. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-0815, reference no. AREN-001CIP.

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REAL PARTY IN INTEREST

The inventors named on this patent application assigned their entire rights to the invention to Arena Pharmaceuticals, Inc.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF CLAIMS

The present application was filed on April 14, 1998, with Claims 1 to 44. During the course of prosecution, Claims 45 to 81 were added and Claims 1 to 33, 35 to 44, 53 to 60, 63 to 68, 70 to 76, 78 and 80 were canceled. Accordingly, Claims 34, 45-52, 61, 62, 69, 77, 79 and 81 are pending, under examination, and stand rejected in the present application. The rejections of Claims 34, 45-52, 61, 62, 69, 77, 79 and 81 are appealed herein.

STATUS OF AMENDMENTS

No amendments to the Claims were filed subsequent to issuance of the Final Rejection.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention is drawn to a method for directly identifying a non-endogenous compound that affects the activity of an endogenous orphan G protein coupled receptor (GPCR). Below is a description of each independent claim appealed herein and where exemplary support for each claim element can be found in the specification.

Independent Claim 69 claims a method for directly identifying a non-endogenous candidate compound as a compound that stimulates an endogenous G protein coupled receptor (GPCR) or reduces the activity of an active receptor state of an endogenous GPCR, where an endogenous ligand for the endogenous GPCR has not been identified (i.e., the GPCR is an orphan GPCR; see specification at: page 18, lines 15 to 21; page 25, lines 22 to 30; and page 30,

lines 1 to 16).

The method includes the steps of:

(a) obtaining a constitutively activated form of the endogenous GPCR, where the constitutively activated GPCR includes a mutation in its amino acid sequence that increases its constitutive activity relative to the endogenous GPCR (see specification at: page 5, lines 10 to 30; page 31, lines 18 to 20; and page 35 lines 19-21);

(b) contacting the non-endogenous candidate compound with the constitutively activated GPCR (see specification at: page 18, lines 13 to 14; and page 33, lines 13 to 19);

(c) analyzing whether the non-endogenous candidate compound is a compound that stimulates the endogenous GPCR or reduces the activity of an active receptor state of the endogenous GPCR, by measuring the ability of the candidate compound to stimulate or inhibit functionality of the constitutively activated GPCR, respectively (see specification at: page 18, lines 3 to 6; and page 18 lines 15 to 21).

Independent Claim 77 claims a method for directly identifying a non-endogenous compound with compound efficacy as to an endogenous orphan GPCR (see specification at: on page 5, lines 10-14 and lines 27-30; page 18, lines 3 to 6; page 31, line 22 to page 32 line 4; and page 35 lines 19-21).

The method including the steps of:

(a) obtaining a constitutively activated form of the endogenous orphan GPCR, where the constitutively activated GPCR includes a mutation in its amino acid sequence that increases its constitutive activity relative to the endogenous orphan GPCR (see specification at: page 5, lines 10-14 and lines 27-30; page 31, line 22 to page 32 line 4; and page 35 lines 19 to 21);

(b) contacting the constitutively activated GPCR with the non-endogenous compound (see specification at: page 18, lines 13 to 14; and page 33, lines 13 to 19);

(c) analyzing the functionality of the constitutively activated GPCR in the presence and absence of the non-endogenous compound (see specification at: page 18, lines 3 to 6; page 19, lines 17 to 19; and page 20, lines 17 to 19); and

(d) identifying the non-endogenous compound as having compound efficacy if the presence of the compound measurably alters the functionality of the constitutively activated GPCR as compared to the functionality of the constitutively activated GPCR in the absence of

the compound (see specification at: page 18, lines 3 to 6; and page 18 lines 15 to 21).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Claims 34, 45-52, 61, 62, 69, 77, 79 and 81 are rejected by the Examiner under 35 U.S.C. § 101 for lacking a patentable utility.

II. Claims 34, 45-52, 61, 62, 69, 77, 79 and 81 are rejected by the Examiner under 35 U.S.C. § 112, first paragraph, for failing to be enabled in view of the asserted lack of patentable utility.

ARGUMENT

I. Claims 34, 45-52, 61, 62, 69, 77, 79 and 81 have a patentable utility under 35 U.S.C. §101.

The Appellants will argue Claims 34, 45-52, 61, 62, 69, 77, 79 and 81 as a single Group under this rejection.

The Utility Examination Guidelines state that Office personnel are to adhere to the following procedures when applying a rejection under 35 U.S.C. §101. Any rejection based on lack of utility should include a detailed explanation as to why the claimed invention has no specific and substantial credible utility.[1] Whenever possible, the Office should provide documentary evidence.[2] In the absence of documentary evidence, the Office must provide a *prima facie* showing that establishes that it is more likely than not that a person skilled in the art would not consider credible any specific and substantial utility asserted by the Applicants for the claimed invention. A *prima facie* showing must contain the following elements: (1) an explanation that clearly sets forth the reasoning used in concluding that the asserted specific and substantial utility is not credible; (2) support for factual findings relied upon in reaching this conclusion; and (3) an evaluation of all relevant evidence of record.[3] A rejection based on lack of utility should not be maintained if an asserted utility for the claimed invention would be

1 Fed. Reg. Vol. 66 at page 1098, Section II-B, paragraph 3.
2 Fed. Reg. Vol. 66 at page 1098, Section II-B, paragraph 3.
3 Fed. Reg. Vol. 66 at page 1098, Section II-B, paragraph 3.

considered specific, substantial, and credible by a person of ordinary skill in the art in view of all evidence of record. [Utility Examination Guidelines, *Federal Register* (Jan. 5, 2001) Vol. 66(4):1092-1099, emphasis added].

The original Congressional intent behind the 1952 Patent Act regarding Section 101 was to ensure that an invention have some identifiable benefit for the public in order to be patentable under §101. This position is supported in *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999), in which the Federal Circuit, relying on *Brenner v. Manson* for support stated that:

> The threshold of utility is not high: An invention is useful under Section 101 if it is capable of providing some identifiable benefit. 51 USPQ2d at 1702.

Based on the above, the Appellants submit that these three words are dispositive to issues under §101: *Some Identifiable Benefit.* In essence, a long line of well-grounded case law has established that under §101, the disclosure need merely provide an indication of usefulness of the invention. The threshold is so low under §101 that it is only when a claimed invention is totally incapable of achieving a useful result or incapable of serving any beneficial end that a rejection can properly be applied, and sustained, under §101.

It is well established that "a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of §101 for the entire claimed subject matter unless there is a reason for the skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer* 183 USPQ 288, 297 (CCPA 1974) (emphasis in original).

In addition to an asserted utility in the specification, an invention can have a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible (see MPEP §2107).

As argued below, Appellants submit that the subject application fully discloses *some identifiable benefit* for the claimed invention, and thus meets (and exceeds) the requirements under 35 U.S.C. §101. Specifically, Appellants contend that the totality of the evidence demonstrates an asserted utility and a well-established utility that are specific, substantial and credible for the claimed invention and that the Examiner has not provided evidence that it is more likely than not that Appellants' statements of utility are false.

The pending claims of the subject application are directed to methods for screening for compounds that stimulate or reduce the activity of an endogenous orphan GPCR (see "Summary of Claimed Subject Matter" above). The claimed methods are applicable to any orphan GPCR of interest to a user that have or be made to have a mutation in its amino acid sequence that increases its constitutive activity relative to the endogenous GPCR. The claims are not, and Appellants submit they should not be, limited to one particular orphan GPCR or to a particular disease or disorder. Rather, the Appellants submit that it is the user of the claimed invention (i.e., one of ordinary skill in the art) that will have in hand an orphan GPCR associated to their satisfaction, e.g., one that is associated with a particular cellular function, disease or disorder.

As discussed in detail in the specification, the traditional study of receptors proceeded from the *a priori* assumption that the endogenous ligand of a receptor must first be identified before discovery could proceed to find compounds that modulate its activity. Thus, at the time of the invention, it was not thought that orphan GPCRs (where, by definition, the endogenous ligand is not known) could be screened to find compounds that modulate the orphan receptor. The subject application discloses methods for screening for modulators of orphan GPCRs using constitutively active forms of the receptors as well as providing a detailed discussion of the utility of such screens (see Description of the Preferred Embodiments section in the application as filed from page 28 to page 35). For example, page 33, lines 17-19 states the "[t]he method of this invention solves a major problem of finding pharmacologically effective compounds for regulation of receptor activity even in the absence of any prior knowledge about the endogenous ligand to the receptor."

On page 4 of the Final Office Action dated September 11, 2009, the Examiner, quoting *In Re Fisher* (76 USPQ2d 1225 (CA FC 2005)), states that:

> ...the U.S. Court of Appeals Federal Circuit stated, "Patent application does not satisfy utility requirement of 35 U.S.C. §101 unless it discloses both "substantial" utility for claimed invention, in form of significant and presently available benefit to public, as well as "specific" utility, which is well-defined and particular benefit to public" (pg 1225) and "an application must show that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. Simply put, to satisfy the "substantial" utility requirement, an asserted use must show that that claimed invention has a significant and presently available benefit to the public" (pg 1230).
>
> In the instant case, the claimed methods lack a specific and substantial utility because there is no specific and substantial utility for a non-endogenous modulatory compound identified by the claimed method. Each orphan GPCR described in the specification for use with the claimed method lacks a specific and substantial utility. Furthermore, identification of a non-endogenous compound that can stimulate (i.e., agonize) or inhibit (i.e., antagonize) the activity of an orphan receptor does not provide a specific and substantial utility for such an identified compound. The specification teaches that such compounds may prove useful without identifying a specific use for the stimulation or inhibition of particular orphan GPCRs. The specification does not provide a reasonable correlation between the activity of any of the orphan GPCRs and a specific and substantial use (e.g., treatment of a disease associated with the activity of the GPCR).

Appellants respectfully submit that the Examiner has erred in his characterization of the requirements for establishing utility of the claimed invention and contend that the claimed invention has a specific and substantial utility.

As indicated above, Appellants note that it is a common misperception that orphan receptors, and by extension compounds that modulate orphan receptors, have no utility. However, knowledge of a GPCR's natural ligand is simply not necessary for establishing a useful function for such a receptor. In fact, it is possible to know a receptor's function and develop and market pharmaceutical agents targeting it without any understanding of the natural ligand which activates it. This general concept is exemplified by the fact that numerous opioids

having analgesic functionality at the mu-opiate receptor were identified and developed long before the first endogenous agonists of that receptor were discovered in 1975.

Indeed, Appellants argued, and provided exemplary publications demonstrating, that prior to the time of filing the present application, orphan GPCRs having a specific function or activity had been identified. Thus, methods for identifying modulatory compounds for such characterized orphan GPCRs, as well as the compounds themselves, would have a specific and substantial utility.

In support of this argument, Appellants provided to the Examiner three different references evidencing this fact (provided herewith in the **Evidence Appendix** as Exhibits A, B and C, respectively): (i) Liao et al., *The Journal of Experimental Medicine* (June 2, 1997) vol. 185, p. 2015-2023, entitled "STRL33, A Novel Chemokine Receptor–like Protein, Functions as a Fusion Cofactor for Both Macrophage-tropic and T Cell Line–tropic HIV-1"; (ii) Alkhatib et al., *Nature* (July 17, 1997) vol. 388, p. 238, entitled "A new SIV co-receptor, STRL33"; and (iii) Farzan et al., *The Journal of Experimental Medicine* (August 4, 1997) vol. 186, p. 405-411, entitled " Two Orphan Seven-Transmembrane Segment Receptors Which Are Expressed in CD4-positive Cells Support Simian Immunodeficiency Virus Infection".

Liao et al. describe the identification of a novel human gene, STRL33, which encodes an orphan GPCR having sequence similarity to chemokine receptors and to chemokine receptor–like orphan receptors. STRL33 is expressed in lymphoid tissues and activated T cells, and is induced in activated peripheral blood lymphocytes. In this reference, Liao et al. demonstrate that, in contrast with the major known cofactors CXCR4 and CCR5, STRL33 can function with CD4 to mediate fusion with cells bearing HIV-1 *Env* proteins from both T cell-tropic and macrophage-tropic HIV-1 strains. Therefore, Liao et al. disclose a human orphan GPCR associated with the infectivity and pathology of the virus that causes AIDS.

Alkhatib et al. describe further studies with the orphan receptor STRL33, this time in studies with simian immunodeficiency virus (SIV). Specifically, Alkhatib et al. show that transfection of STRL33 into Jurkat cells renders them competent for infection with SIV,

demonstrating that this orphan receptor is a co-receptor for SIV. This activity has relevance to human AIDS apart from the general parallels between the human and simian systems, as SIV is phylogenetically thought to be the immediate progenitor of HIV-2, a virus known to cause AIDS in humans. Additionally, this study provides clues to understanding how individuals who are homozygous for an inactivating deletion in the CCR5 gene, and therefore thought to be resistant to HIV infection, are nonetheless infected with HIV-1. Specifically, HIV may rely on alternative co-receptors, including orphan receptors like STR33.

Farzan et al. disclose that two orphan seven-transmembrane receptors, gprl and gpr15, serve as coreceptors for SIV, and are expressed in human alveolar macrophages. Farzan et al. go on to find that gpr15 (the more efficient SIV coreceptor of these orphan receptors) is also expressed in human CD4 + T lymphocytes and activated rhesus macaque peripheral blood mononuclear cells. These results underscore the potential diversity of seven-transmembrane receptors that are used as entry cofactors by primate immunodeficiency viruses, including orphan receptors gpr1 and gpr15.

On page 10 of the Final Office Action dated September 11, 2009, the Examiner, in response to the above arguments, asserts that "[t]he known function of STRL33, gprl and gprl5 as co-factors for retroviral entry into cells does not provide a specific and substantial utility of the modulators identified by the claimed method." In making this assertion, the Examiner states that: 1) the specification does not provide a link between the modulators of the claimed invention and the role of STRL33, gprl and gprl5 in retroviral co-entry; 2) the receptors are not disclosed in the instant specification; and 3) the use of modulators in blocking retroviral entry is not taught as a utility for modulators of the instant invention.

Appellants submit that the knowledge in the art of orphan GPCRs having a known activity or cellular function provides a *well-established* utility for the claimed invention, and thus need not be disclosed in the specification. Thus, the Examiners statements of the deficiencies *in the specification* in disclosing STRL33, gprl and gprl5 as co-factors for retroviral entry into cells is immaterial to Appellants arguments supporting the well-established utility of the claimed invention. Current law is clear that a patent does not have to include everything known in the art

at the time of filing. Indeed, as stated in Hybritech Inc. v. Monoclonal Antibodies, Inc. 802 F.2d 1367, 1384 (Fed. Cir. 1986) "[A] patent need not teach, and preferably omits, what is well known in the art." Thus, the Examiners position that Appellants' argument with regard to STRL33, gprl and gprl5 receptors are insufficient because these receptors are not described in the specification is in error.

The Examiner goes on to assert that STRL33, gprl and gprl5 are not receptors encompassed by the claims at the time of filing because they are not orphan GPCRs. The Examiner states that CD4 is an endogenous ligand for these receptors, arguing that because the gp120/CD4 complex is "specific" for these receptors, and CD4 is an endogenous molecule, it represents an endogenous ligand as thus renders the STRL33, gprl and gprl5 receptors not orphan receptors (and thus outside the bounds of the claimed invention).

Appellants respectfully disagree with this characterization of the relationship between CD4 and the STRL33, gprl and gprl5 receptors. As specified on page 20, lines 6-7 of the specification as filed, an orphan receptor is defined as "an endogenous receptor for which the *endogenous ligand specific for that receptor* has not yet been identified or is not known" (emphasis added). Appellants submit that the fact that a virus, which is a non-endogenous entity, employs CD4 as a primary receptor and one of the above-cited orphan GPCRs as a co-receptor does not mean that CD4 is the "endogenous ligand specific for that receptor". Nowhere is *CD4 alone* shown to bind specifically to any of these receptors. Moreover, none of the cited references state that CD4 is the endogenous ligand for the orphan receptors described therein. Thus, Appellants maintain that the STRL33, gprl and gprl5 receptors are indeed orphan receptors, even after their identification as co-receptors for CD4-tropic viruses.

Appellants further note that the specification provides a teaching for associating receptors and diseases or disorders. For example, see page 33, line 20, to page 34, line 12 and page 75, line 20, to page 76, line 1, excerpts from which are provided below:

> Once it has been appreciated that: 1) inverse agonists to orphan receptors can be identified-by the methodologies of this invention; and 2) that such inverse agonists are ideal candidates as lead compounds in drug discovery programs for treating diseases related to the receptors, a search, impossible in the prior art, for treatments to diseases becomes

> enabled by this knowledge. For example, scanning both diseased and normal tissue samples for the presence of a receptor now becomes more than an academic exercise or one which might be pursued along the path of identifying an endogenous ligand... The presence of the receptor in a diseased tissue, or the presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue strongly can be preferably utilized to identify a correlation with that disease.

The data support the position that the present invention effectively and efficiently allows for direct identification of inverse agonists against a receptor for which the endogenous ligand is unknown. Because of this technology, correlating the distribution of orphan receptors in specialized tissue and/or correlating the presence of such receptors with specified diseases allows for a rational approach to the development of a pharmaceutical composition(s) for such diseases.

On the bottom of page 8 of the Final Office Action dated September 11, 2009, the Examiner states that "[t]he disclosure of an orphan GPCR with a specific cellular process in the instant specification could possibly provide a specific and substantial utility for the claimed invention". The Examiner goes on to state "however, it is maintained that the instant application at the time of filing does not identify any such GPCRs."

Appellants contend that the specification describes an example of an orphan GPCR (GPR3) that is associated with a disease (epilepsy). Figure 15 of the present application, which is described in Example 4 (see page 75, lines 4-6), shows that the orphan receptor GPR3 is more highly expressed in neuronal tissue from the temporal lobe of individuals with epilepsy as compared to individuals not suffering from this condition. Thus, the expression of GPR3 has been associated with a disease condition, and as such a method of screening for compounds having modulatory activity has a clear utility.

Appellants again stress that to support the utility of the subject invention, the "disclosure of an orphan GPCR with a specific cellular process" may be either in the specification as filed or well-know in the art at the time of filing the application. As discussed in detail above, such orphan receptors had been described in the art (e.g., STRL33, gpr15 and gpr1) as well as in the specification (GPR3). The existence of such orphan receptors with known function or activity does make the claimed invention useful.

Appellants further contend that a person skilled in the art would not make the effort to screen an orphan GPCR if they did not have some use for the compounds identified by the screening method. As noted above, Appellants contend that the claimed screening assay has a specific and substantial "real world" use because it allows a user to identify, from a library of candidates, specific compounds that have a defined modulatory activity for an orphan GPCR of interest, regardless of the reason for why it is of interest to a user. This utility is clearly described throughout the application as providing researchers in the field with a novel approach to by-pass the significant bottle-neck in the orphan GPCR field, i.e., waiting for an orphan GPCR to be "de-orphanized" prior to conducting further functional studies. In view of this, Appellants submit that those of ordinary skill in the art would consider the claimed invention to have a particular and immediate use.

The claims of the subject application can be considered a "research tool" or enabling technology which plays an important role in developing a biopharmaceutical end product (compounds), where without it, the end product would either not have been found or found only after a great deal of effort and expense. As of the filing date of the invention, orphan receptors were not screened until they had been "de-orphanized" (i.e., an endogenous ligand had been identified). However, finding an endogenous ligand for an orphan receptor was, and still is, very expensive, time consuming and oftentimes unsuccessful. The claimed methods provide a novel and inventive way to screen for compounds that modulate an orphan receptor's activity without first de-orphanizing the receptor (i.e., identifying the endogenous ligand).

With regard to the utility of research tools, MPEP 2107.01(C), under the heading "Research Tools", states the following:

> C. Research Tools
> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, *screening assays*, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds).

(emphasis added)

As explicitly stated above, research tools that are used in a research or laboratory setting, *including screening assays as claimed in the present invention*, have "a clear, specific and unquestionable utility." In the case of the subject invention, the screening assay method identifies compounds that have modulatory activity on an orphan GPCR of interest. In one embodiment, these compounds can be employed in a predictable manner as reagents that have a known effect on the orphan GPCR (i.e., as agonists or inverse agonists).

The ability to use the claimed methods on any orphan receptor demonstrates the real world usefulness of this invention. In fact, the Assignee of the subject application, Arena Pharmaceuticals, was able to raise venture capital for research based on this technology (called CART for constitutively activated receptor technology). Appellants provide herewith as Exhibit D a press release dated February 22, 1999, which announces successful completion of a $17 million private offering. In the press release Arena's president and CEO is quoted as saying "we view the substantial over-subscription for our Series D Preferred Stock as a good indication of the support that our investors have in Arena and our CART™ Technology". The press release goes on to further describe the CART technology.

Appellants also provide as Exhibit E another press release from November 15, 1999, announcing a collaboration between Arena Pharmaceuticals and Neurocrine Biosciences for use of Arena's constitutive activation technology to three orphan GPCRs. A quote form the vice president of drug discovery at Neurocrine Biosciences indicates that "Orphan receptors provide great opportunities for new discoveries in biology and neuroscience and can become novel drug targets. Neurocrine has discovered several orphan receptors and Arena's proprietary technology will allow us to maximize our evaluation of these potential drug targets and provide strategies to screen these receptors for small molecule agonists and antagonists."

Clearly, both investors and other biotechnology companies appreciated the "real world" utility of the claimed invention as implemented in Arena's CART technology.

In further support of the utility of the claimed invention, Appellants provide herewith a copy of claims that have been granted in the European counterpart to the subject application (Exhibit F). The granting of these claims, which closely track those in the subject application, indicates that the European Patent Office considers them to have clear industrial applications (i.e., to have utility).

In continuing to maintain this rejection, the Examiner essentially is asserting that more research is needed to identify a specific and substantial use for the modulatory compounds identified in the claimed screening method. Appellants disagree. Again, the subject claims are drawn to screening assays for identifying a compound having a specific activity, i.e., having a modulatory activity for an orphan receptor of interest to the user. Such compounds have as much immediate utility as would the endogenous ligand for the receptor. Specifically, as with the endogenous ligand, the compounds identified in the claimed screening assay can be employed in a predictable manner as reagents that have a known effect on the orphan GPCR (e.g., as agonists or inverse agonists). While performing further experiments on these compound may be done (e.g., to identify a therapeutic application for one or more of the identified compounds) this is not required for the claimed screening methods to have utility.

Appellants submit that, similar to the situation with sequencing assays and/or PCR assays, the user of the claimed screening assay determines which specific entity is the subject of the analysis (i.e., which specific orphan GPCR is to be employed to identify modulatory compounds). The reasons for why a user wants to screen for modulatory compounds for a particular orphan GPCR will vary, including its activity in a specific cellular process (e.g., a disease process, like viral entry) as well as having an expression pattern of particular interest (e.g., in a specific diseased tissue or cells at a specific developmental stage). However, regardless of why a user is interested in a particular orphan GPCR, Appellants submit that the MPEP citation above clearly and explicitly states that screening assays have "a clear, specific and unquestionable utility."

In addressing the arguments above, the Examiner states the following:

> With respect to 'sequencing assays' and 'PCR assays', Applicants do not identify a specific granted patent with claims which are analogous to the instant

> claims. DNA sequencing and PCR were developed long before the publication of the revised Utility Examination Guidelines 1/5/01 in the Federal Register. It is noted that at the time of invention of PCR in 1983, many nucleic acid sequences existed that either had utility as markers or to encode specific proteins with utility. Thus, at the time of invention, PCR had immediate utility in producing large quantities of identical copies of nucleic acids with specific and substantial utility. In contrast, the instantly claimed methods are limited solely to identifying non-endogenous modulators of "orphan GPCRs" (i.e., a GPCR for which an endogenous ligand has not been identified). There is no specific and substantial utility for any of the non-endogenous compounds identified by the claimed methods. Further research would be required to identify a use for any of the modulators identified by the claimed methods. Applicants' claimed methods are analogous to a gene chip in which none of the genes on the chip is a characterized gene. In general, gene chips are commercially successful and the skilled artisan would believe them to be useful. However, a gene chip would not meet the utility requirement if none of the genes on the chip had a specific and substantial utility.

First, Appellants note that the arguments regarding sequencing and PCR were not in reference to a specific patent or set of claims drawn to those methods. Rather, Appellants were demonstrating that one utility of the claimed method is found in its ability to identify modulatory compounds for *any* orphan GPCR of interest to a user, just as sequencing assays and PCR are extremely useful in that they can be applied to any polynucleotide of interest to the user. This general statement of utility was not being applied by Appellants to a specific patent or set of claims for sequencing or PCR methods.

Second, as argued above, it is simply inaccurate to assert that "[t]here is no specific and substantial utility for any of the non-endogenous compounds identified by the claimed methods" becuase orphan GPCRs *have* been associated with specific functions or cellular processes, as detailed in the specification as filed *and* as known in the art at the time of filing the applicaiton (as agued above). This is true regardless of the current status of the receptor, i.e., if it has since been de-orphanized by identification of its endogenous ligand.

Third, Appellants submit that the analogy of a gene chip, in which none of the genes on the chip is a characterized gene, with the claimed invention does not support the Examiner's position. Appellants contend that the asserted *possibility* of producing a gene chip with no characterized genes in no way negatively impacts the broad utility of gene chips. In other words,

the mere existence of species of a claimed invention that might fail a specific test of utility does not mean that the entire generic claim lacks utility. Moreover, Appellants submit that orphan GPCRs are not akin to uncharacterized genes, as asserted by the Examiner, because orphan GPCRs can and have been characterized, as detailed in the arguments above. Again, Appellants contend that the claimed screening methods are useful because orphan receptors have been identified that are associated, for example, with an activity, disease or cellular function.

Based on the discussion above, Appellants contend that the claimed invention is supported by both an asserted utility and a well-established utility that are specific, substantial and credible, and that the Examiner has erred in rejecting the claimed invention as lacking utility. Because the claimed invention has a significant and presently available useful benefit to the public, Appellants respectfully request reversal of this rejection under 35 U.S.C. §101.

II. Claims 34, 45-52, 61, 62, 69, 77, 79 and 81 are enabled under 35 U.S.C. §112, first paragraph.

The Appellants will argue the claims as a single Group.

The Examiner has stated that since the claimed invention is assertedly not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention without undue experimentation.

Appellants submit that the rejection of the claims for lack of utility has been adequately addressed in the arguments in the preceding section of this Appeal Brief (i.e., Appellants arguments in support of utility of the claimed invention under 35 U.S.C. § 101).

Appellants thus respectfully request reversal of the rejection of the claims as unpatentable under 35 U.S.C. §112, first paragraph.

RELIEF REQUESTED

The Appellants respectfully request that the rejections of Claims 34, 45-52, 61, 62, 69, 77, 79 and 81 under 35 U.S.C. §101 and §112, first paragraph, be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: October 8, 2010

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CLAIMS APPENDIX

34. The method of claim 69 or 77 wherein the compound is determined to be a compound that reduces the activity of an active receptor state of said constitutively activated GPCR.

45. The method of claim 69 or 77 wherein the third intracellular loop of the constitutively activated GPCR comprises the following sequence:

X1BBHyX2

wherein X1 is an amino acid; B is a basic amino acid; Hy is a hydrophobic amino acid; and X2 is an amino acid.

46. The method of claim 45 wherein X1 is glycine.

47. The method of claim 45 wherein X1 is lysine.

48. The method of claim 45 wherein Hy is alanine.

49. The method of claim 45 wherein X2 is lysine.

50. The method of claim 45 wherein X2 is arginine.

51. The method of claim 45 wherein X2 is glutamic acid.

52. The method of claim 69 or 77 wherein the second intracellular loop of the constitutively activated GPCR comprises the following sequence:

XRY

wherein X can be any amino acid other than aspartic acid; R is arginine; and Y is tyrosine.

61. The method of claim 45 wherein the sequence XlBBHyX2 is an endogenous

sequence.

62. The method of claim 52 wherein the sequence XRY is an endogenous sequence.

69. A method for directly identifying a non-endogenous candidate compound as a compound that stimulates an endogenous G protein coupled receptor (GPCR) or reduces the activity of an active receptor state of an endogenous GPCR, wherein an endogenous ligand for said endogenous GPCR has not been identified, said method comprising the steps of:

(a) obtaining a constitutively activated form of said endogenous GPCR, wherein said constitutively activated GPCR comprises a mutation in its amino acid sequence that increases its constitutive activity relative to said endogenous GPCR;

(b) contacting the non-endogenous candidate compound with said constitutively activated GPCR;

(c) analyzing whether said non-endogenous candidate compound is a compound that stimulates said endogenous GPCR or reduces the activity of an active receptor state of said endogenous GPCR, by measuring the ability of the candidate compound to stimulate or inhibit functionality of said constitutively activated GPCR, respectively.

77. A method for directly identifying a non-endogenous compound with compound efficacy as to an endogenous orphan GPCR, the method comprising the steps of:

(a) obtaining a constitutively activated form of said endogenous orphan GPCR, wherein said constitutively activated GPCR comprises a mutation in its amino acid sequence that increases its constitutive activity relative to the endogenous orphan GPCR;

(b) contacting the constitutively activated GPCR with the non-endogenous compound;

(c) analyzing the functionality of the constitutively activated GPCR in the presence and absence of the non-endogenous compound; and

(d) identifying the non-endogenous compound as having compound efficacy if the presence of the compound measurably alters the functionality of the constitutively activated GPCR as compared to the functionality of the constitutively activated GPCR in the absence of the compound.

79. The method of claim 77, wherein said functionality of the constitutively activated GPCR is binding to GTP.

81. The method of claim 69 or 77, wherein said method is performed in a laboratory or research setting.

EVIDENCE APPENDIX

Appellants provide copies the following Exhibits:

A. Liao et al., *The Journal of Experimental Medicine* (June 2, 1997) vol. 185, p. 2015-2023, entitled "STRL33, A Novel Chemokine Receptor–like Protein, Functions as a Fusion Cofactor for Both Macrophage-tropic and T Cell Line–tropic HIV-1".

B. Alkhatib et al., *Nature* (July 17, 1997) vol. 388, p. 238, entitled "A new SIV co-receptor, STRL33".

C. Farzan et al., *The Journal of Experimental Medicine* (August 4, 1997) vol. 186, p. 405-411, entitled " Two Orphan Seven-Transmembrane Segment Receptors Which Are Expressed in CD4-positive Cells Support Simian Immunodeficiency Virus Infection".

D. Press release dated February 22, 1999.

E. Press release dated November 15, 1999.

F. Copy of claims that have been granted in the European counterpart to the subject application.

RELATED PROCEEDINGS APPENDIX

As stated in the *Related Appeals and Interferences* section above, there are no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal. As such this section is left blank.